III. Claims 48-49 and 70-74, drawn to a molecule comprising functional variants of first and second ligand linked by a covalent bond.

Applicants were further requested to make a series of species elections in each group.

Applicants hereby elect the invention of Group I (claims 1-43 and 50-68) for examination in the present application, with traverse.

In order to comply with the election of species requirement, Applicants make the following species elections:

Subgroup 1: Species of target biological molecule - caspase 3, where the nucleophile is a thiol, which is associated with a cysteine (Cys). This election is supported at least in Example 3 and 4. Claims 1-6, 8-43, 50-59, and 64-67 read of this species.

Subgroup 2: Species of ligand candidate (claim 1) - A member of the disulfide library described in Example 1. Claims 1-43, 50-59, and 64-67 read on this species. Applicants disagree with the Examiner's assertion that for the election to be complete, it should include the complete chemical structure of the ligand candidates. The screening method of the invention is directed to the identification of ligand candidates that have affinity for a first and a second site of interest on a Target Biological Molecule (TBM). In order to identify the latter, structurally, the only requirement is that the ligand candidates contain a functional group capable of reacting with the "second functional group" on the small molecule extender (SME). Once this requirement is met, the method can be performed, regardless of the core structure of the ligand candidates screened. Accordingly, the shared structure by the ligands elected is that they are all disulfide compounds.

Subgroup 3: Species of small molecule extender - 2,6-dichloro-benzoic acid 3-(2-acetylsulfanyl-acetylamino)-4-carboxy-2-oxo-butyl ester. This election is supported at least by Example 2. Claims 1-43, 50-69, and 64-67 read on this species.

Subgroup 4: Species of conditions: Thiol exchange with dithiothreitol. Support for this election is at least in original claim 16. Claims 1-43, 50-59, and 64-67 read on this species.

Subgroup 5: Species of irreversible covalent group: Thiol group. Support for this election is provided throughout the specification, including paragraph [0077]. Claims 1-43, 50-59, and 64-67 read on this species.

Subgroup 6: Species of reaction that SME can undergo: Michael-type adduct with the thiol. Support for this election is at least in original claim 18. Claims 1-43 and 50-68 read on this species.

Subgroup 7: Species of first functional group: α-halo acid. Support for this election is, for example, in paragraph [0082]. Claims 1-25, 33-43, and 50-68 read on this species.

Subgroup 8: Species of small organic ligand candidates (claim 20): A member of the disulfide library described in Example 1. Claims 1-43, 50-59, and 64-67 read on this species. Just as before, Applicants disagree with the Examiner's assertion that the election, in order to be responsive, should include the complete chemical formula of the small organic ligand candidates. The screening method of the invention is directed to the identification of ligand candidates that have affinity for a first and a second site of interest on a Target Biological Molecule (TBM). In order to identify the latter, structurally, the only requirement is that the ligand candidates contain a functional group capable of reacting with the "second functional group" on the small molecule extender (SME). Once this requirement is met, the method can be performed, regardless of the rest of the chemical structure of the ligand candidates screened. Accordingly, applicants submit that the present election should be accepted as responsive.

Subgroup 9: Species of conditions for step (v): dithiothreitol. For support, see, e.g. original claim 23. Claims 20-43 read on this species.

Subgroup 10: Species of identification: mass spectrometry. Support for this election is at least in paragraph [0111] of the specification. Claims 1-34; 36-37; 39-43; and 50-68 read on this species.

Subgroup 11: Species of detectable tag: Fluorescent label. Support for this election is at least at page 50, paragraph [0112] of the specification. Claims 1-33; 35-36; 38-43; and 50-68 read on this species.

Subgroup 12: Species of covalently linked ligands (claim 39): The "monophore" shown in Figure 5, and the small molecule present in the peak of 17,094 in the mass spectrum shown in Figure 6. Claims 1-46, and 50-68 read on this species. Since this requirement requests the election of ligands the identity of which is determined only as a result of performing the screening assay of the present invention, Applicants disagree with the Examiner's assertion that the election should include the entire structure of the covalently linked ligands. The screening method of the invention is directed to the identification of ligand candidates that have affinity for a first and a second site of interest on a Target Biological Molecule (TBM). Structurally, the only requirement is that the ligand candidates contain a functional group capable of reacting with the "second functional group" on the small molecule extender (SME). Once this requirement is met, the method can be performed and repeated, regardless of the core structure of the ligand candidates screened. The ligands identified can then be linked to each other to provide structures with enhanced binding affinity.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39750-0001A. Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: February 10, 2004

Ginger R. Dreger
Reg. No. 33,055

HELLER EHRMAN WHITE & McAULIFFE LLP
Customer No. 25213
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 2005961 v1
2/10/04 8:30 AM (39750.0001)